The platelet EP3 receptor for PGE2 facilitates platelet aggregation in response to multiple agonists. Analysis of the platelet signaling cascade suggests that the EP3 receptor for prostaglandin E2 (PGE2) represents a novel target for preventing acute thrombosis in cardiovascular disease. We successfully employed a ligand-based design strategy to develop potent antagonists of PGE2 binding to EP3. The combined SAR and in vitro/ex vivo studies yielded lead molecule (E)-3-(1-(2,4-dichlorobenzyl)-5-fluoro-3-methyl-1H-indol-7-yl)-N-(4,5-dichlorothiophen-2-ylsulfonyl)acrylamide designated DG-041 as our clinical lead. DG-041 was well tolerated in pre-clinical safety pharmacology and 3 month chronic toxicity studies in rat (up to 150 mg/kg) and dog (up to 20 mg/kg) following oral dosing. There was no evidence of bleeding in any vascular bed during the in-life phase of the study or by histopathological examination. DG-041 was not genotoxic in AMES or in-vitro micronucleus assays. We further show in human Phase I clinical studies, that at doses of DG-041 that in human subjects efficiently block PGE2 facilitated platelet responses ex vivo, there is no impact on bleeding time. Thus, studies in rats, mice and human volunteers suggest that an EP3 antagonist has the potential to improve anti-platelet therapy in MI and stroke, where control of pathogenic thrombosis is the therapeutic goal, while minimally impacting haemostatic thrombosis, which limits the benefit of current anti-platelet therapy.